REMARKS

Upon entry of the foregoing amendment, claims 1, 2, 5-7, 9, 10, 13-17, 28, 71, 73-85 are pending in the application, with claims 1, 16, 73-81, and 84 being the independent claims. Claims 1, 2, 10, 15, 16, 73, and 78-83 are sought to be amended. Claims 84 and 85 are newly presented. Claims 3, 4, 8, 11, 12, 18-27, 29-70, and 72 were cancelled by previous amendment without prejudice to or disclaimer of the subject matter therein. The Examiner had previously withdrawn claims 73-79 and 81-83 in his last office action. Applicants' reserve all their rights to pursue the allowance of the subject matter of the withdrawn claims in a separate patent application.

Claims 1 and 16 have been amended to change the recited upper limit from about 20 mg/kg to about 8 mg/kg. Claims 10, 15, 79 and 80 have been amended to correct a typographical errors, for example, in claim 10, by deleting the incorrectly spelled "(S)-noreketamine" and inserting the correctly spelled "(S)-norketamine." Claims 1, 2, 10, 73, and 78-83 have been amended to delete the phrase "substantially enantiomerically pure" immediately prior to "(S)-norketamine." Claim 16 has also been amended to add rectal, vaginal, and ocular as additional routes of administration. Support for these changes can be found in the specification as originally filed, e.g., at pages 11 and 12, paragraphs [0026] and [0027], and at page 20, paragraph [0052].

These changes are believed to introduce no new matter, and their entry is respectfully requested. Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Statement of the Substance of the Interview

The undersigned attorney wishes to thank Examiner Chong for the in-person interview held at the United States Patent and Trademark Office on November 13, 2008, in which a discussion about this application and the pending claims took place among Dr. Chong, Mr. Robert Alonso, Dr. Mark Kleven, Dr. Peter Crooks, and the undersigned attorney. During the discussions, the participants explored the alleged bases or support of the Examiner's rejection, and the propriety of the Examiner's combination of two cited references (Harbut *et al.* in view of Ebert *et al.*). Applicants pointed out what they believed one of ordinary skill in

the art would understand the contents of the two cited references to mean, what significance the evidence described in the previously submitted Kleven Rule 132 Declaration holds on the issue of unexpected results, and a proposed amendment to lower the upper numerical limit recited in independent claims 1 and 16 to a value that is not disclosed, taught or suggested by the two cited references, either alone or in combination with one another.

The Examiner is respectfully invited to call the undersigned attorney if any issues arise that would warrant further discussion.

Claim Rejections Under 35 U.S.C. §103

Claims 1-2, 5-7, 9-10, 13-17, 28, 71, and 80 stand rejected under 35 U.S.C. §103(a) for allegedly being obvious over US Patent Application 2005/0148673 ("Harbut *et al.*") in view of Ebert *et al.*, European Journal of Pharmacology, Aug. 20, 1997, 333 (1):99-104, ("Ebert *et al.*"). This rejection is respectfully traversed for the reasons provided below.

The Examiner maintains that it would have been *prima facie* obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to have substituted substantially enantiomerically pure (S)-norketamine as disclosed by Ebert *et al.* for the ketamine in the method of treating neuropathic pain as disclosed by Harbut *et al.* (Office Action, at page 4, lines 14-17.)

I. The Examiner's Proposed Combination of Harbut *et al.* and Ebert *et al.* is Improper Because Neither Reference Provides a Proper Motivation to Replace the Racemic Ketamine of Harbut *et al.* with (S)-Norketamine of Ebert *et al.*

In the Office Action, the Examiner makes several statements concerning the alleged teachings of Harbut *et al.*, including admitting that norketamine, the metabolic product of ketamine, is "about 25% as effective as ketamine (paragraph 0081)." (Office Action at page 3.) Indeed paragraph 0081 of Harbut *et al.* states that:

> [0081] Intravenous infusion is regarded as the preferable mode of administration, since (i) it can avoid the types of adverse skin-related side effects that were reported in Eide et al 1995, and (ii) *it can also maximize the effects that can be exerted by the ketamine before it is metabolically degraded into metabolites such as norketamine, which is only about 25% as effective as ketamine in*

> *reducing pain signals*. Alternate modes of administration may be discovered to be effective, for some types of pain treatments, after sufficient clinical trial data are gathered in the future; however, any initial clinical trials preferably should use intravenous infusion, while the boundaries and limits of this type of treatment are being evaluated. (emphasis added)

Thus, one of ordinary skill in the art reading the passage of Harbut *et al.*, referred to by the Examiner, himself, would reasonably come away with the notion that ketamine should be administered to a patient in such a way so as to maximize its effects by avoiding a first pass effect, which metabolizes ketamine to norketamine, a substance having only about 25% of the effectiveness of ketamine in reducing pain signals. If the objective in altering a neuropathic pain condition, as taught by Harbut *et al.*, is to keep ketamine from being converted to norketamine – why would one of ordinary skill in the art actually *replace* ketamine *with* norketamine (let alone (S)-norketamine, which is not mentioned at all in Harbut *et al.* as the Examiner has already acknowledged) as proposed by the Examiner? Clearly, Harbut *et al.* not only fails to provide any motivation for such a replacement, this reference actually *teaches away* from making such a replacement.

Turning now to the disclosure of Ebert *et al.*, this reference purports to study the characteristics of certain compounds in tritiated MK-801 binding assays using suspensions of rat brain homogenates and in electrophysiological test systems using rat cortical wedge and neonatal rat spinal cord preparations, both binding assays and electrophysiological test systems being *in vitro* assays. The compounds tested included the enantiomers of ketamine and norketamine, MK-801 and phencyclidine. See, Ebert *et al.*, page 100, upper left-hand column. Seeking to dispel a notion that the principal metabolite of ketamine is inactive ("Thus, the clinical effects of ketamine [have] been ascribed to the parent compound, whereas the metabolite has been considered inactive." At page 103, upper left-hand column.), the authors of this reference state that:

> We therefore conclude that the main metabolite of (S)-ketamine, (S)-norketamine, acts as a weak non-competitive NMDA receptor antagonist in the rat cortex and spinal cord. *Following oral administration of (RS)-ketamine, (S)-norketamine will be present in human plasma at sufficiently high concentrations to account for some of the observed analgesic activity.* Clinical studies are now under way to investigate whether orally

> administered (S)-norketamine may have fewer side effects than (S)-ketamine.

At page 103, upper right-hand column (emphasis added). Before addressing the specific assertions made by the Examiner concerning this reference, Applicants would like to respectfully point out that the specific "conclusion" reached by the authors of this reference, which is depicted in italics, above, is one that is completely unsupported by the work of the authors presented in this reference, which is limited to experiments using *in vitro* assays only. To reiterate, these authors conducted no *in vivo* experiments, let alone clinical studies using oral administration of any compounds of interest. Properly viewed in this context, the "conclusions" expressed by these authors, beyond the first sentence reproduced above, are more properly described as *predictions*, at best, or worse *wishful thinking*. Indeed, there appears to be no evidence that the statement these authors make in the last sentence of the paragraph reproduced above is even accurate. Eleven years after the publication of this reference, Applicants are unaware of any evidence that the purported clinical studies "now under way" were ever initiated let alone completed.

Accordingly, Applicants respectfully submit that one of ordinary skill in the art would attach little to no weight to the purported "conclusions" reached by the authors of this reference – beyond the first sentence of the paragraph reproduced above. Thus, no reasonable expectation of success can be attributed to the purported use of (S)-norketamine as an analgesic.

In particular, one of ordinary skill in the art would recognize that Ebert *et al.* does not stand for the proposition that: (i) (S)-norketamine contributes significantly to the clinical activity of (S)-ketamine, let alone (RS)-ketamine, or (ii) (S)-norketamine is known to have fewer side effects than ketamine. Moreover, the tritiated MK-801 binding and electrophysiology studies performed by the authors of this reference assessed the binding affinities of the compounds of interest relative to MK-801 and NMDA. Although the authors use the terms "potent" or "potency," the authors' statements reflect the relative strength or weakness of the compounds tested in terms of binding to receptor molecules present in the *in vitro* assays. As Applicants are aware, one cannot confidently draw a direct correlation between the results of these *in vitro* binding assays and the actual potency of the same compounds to illicit a physiological or pharmacological response in an *in vivo* setting. The

tritiated MK-801 binding experiments with S-ketamine and R-ketamine simply determine affinity of these compounds for the binding site on the NMDA receptor, and do not provide any information on the functional response elicited by these compounds at the receptor. Thus, the authors would not be able to ascertain from the results of the binding experiments if S-ketamine was a receptor agonist or an antagonist, and similarly, or if R-ketamine was a receptor agonist or antagonist. Therefore, just because the authors state that (S)-ketamine was approximately five times more "potent" than (R)-ketamine as an inhibitor of tritiated MK-801 binding *in vitro*, it does not mean that (S)-norketamine, as a potential drug for humans, is actually five times *as potent* as the opposite enantiomer.

The Examiner has attributed to Ebert *et al.* certain teachings, with which Applicants respectfully disagree. In view of the discussion presented above, Applicants cannot accept as true the Examiner's statements that:

> It was determined that (S) norketamine contributes significantly to the clinical activity of (S) ketamine (abstract);
>
> It was also determined that (S)-norketamine is approximately 8 times more potent than (R)-norketamine (pg. 102);
>
> Following oral administration of (RS)-ketamine, (S)-norketamine will be present in human plasma at sufficiently high concentrations to account for some of the observed analgesic activity;
>
> Clinical studies involving oral administration of (S)-norketamine and its reduced side effects are now being investigated in humans.

Office Action, at page 4. Consequently, Applicants respectfully traverse the Examiner's contention that it would have been *prima facie* obvious to a person of ordinary skill in the art to have substituted substantially pure (S)-norketamine as disclosed by Ebert *et al.* for the ketamine in the method for treating neuropathic pain as disclosed by Harbut *et al.* because not only do the cited references fail to provide a motivation for the proposed substitution, the cited references fail further in that they do not provide one of ordinary skill in the art with a reasonable expectation of success. Indeed, as discussed above, at least one of the cited references *teaches away* from making the substitution proposed by the Examiner, while the other offers, at best, thinly supported *predictions*.

II. Even if *Arguendo* the Examiner's Proposed Combination of Harbut *et al.* and Ebert *et al.* is Deemed Proper, the Alleged Obviousness is Overcome by Applicants' Unexpected Finding of Lower Side Effects When (RS)-Ketamine is Compared with (S)- or (R)-Norketamine at Equipotent Dosage Levels

In the Office Action, the Examiner dismissed Applicants' evidence of unexpected results, as previously presented in the Rule 132 Declaration by Dr. Mark Kleven. In particular, the Examiner states that Applicants' assertion of an unexpected reduction of side effects by (S)-norketamine "is incorrect because this property is known in the prior art, therefore considered to be expected." (Office Action, at page 6, lines 13-14.) In addition, the Examiner states that the Ebert *et al.* reference "teaches that clinical studies involving oral administration of (S)-norketamine are accompanied with reduced side effects in humans," and concludes that because "(S)-norketamine is already known for its reduced side effects, therefore the Kleven Declaration shows nothing unexpected." (Office Action, at page 6, lines 15-18.) For the reasons discussed extensively by Applicants, above, Ebert *et al.* provide no support for the Examiner's statements and conclusion that clinical studies involving oral administration of (S)-norketamine are known and have shown reduced side effects. The only teaching that is actually supported by the work presented in Ebert *et al.* is that (S)-norketamine acts as a weak non-competitive NMDA receptor antagonist in the rat cortex and spinal cord *in vitro* assays.

In the hands of Applicants, and as described in the Kleven Declaration, *in vivo* experiments involving the intraperitoneal administration in rats of racemic ketamine, (S)-norketamine, and (R)-norketamine have shown that one has to administer about twice as much (S)-norketamine (16 mg/kg) and about four times as much (R)-norketamine (32 mg/kg) to achieve the same antihyperalgesic effects as racemic ketamine administered at a dosage of 8 mg/kg. (See, FIG. 1 of the Kleven Declaration, which shows that to achieve an approximately maximal level of antihyperalgesic effect in an *in vivo* rat model, one has to administer about 8 mg/kg of racemic ketamine, about 16 mg/kg of (S)-norketamine, and about 32 mg/kg of (R)-norketamine.) Because of the apparent differences in potency between these three compounds, one of ordinary skill in the art would have expected that the administration of *equal* amounts (e.g., 8 mg/kg of each) of racemic ketamine, (S)-norketamine, and (R)-norketamine would have resulted in a decreasing pharmacologic effect,

which would have been accompanied by a similar decrease in observed side effects (in the present case, ataxia, stereotypic behavior, and activity level). If Applicants had presented data from *in vivo* experiments involving the administration of *equal* amounts of these three compounds, then Applicants agree that one of ordinary skill in the art would have expected a tendency toward a decrease in side effects in going from racemic ketamine to (S)-norketamine and to (R)-norketamine. However, the data presented in the Kleven Declaration is *not* about administering *equal* amounts of these three compounds, it is about administering *equipotent* amounts of these three compounds.

Having administered approximately twice as much (S)-norketamine and approximately four times as much (R)-norketamine compared to racemic ketamine, one of ordinary skill in the art would have expected the *same* level of pharmacologic effect (FIG. 1, Kleven Declaration) and the *same* level of side effects between the three sets of experiments. As strikingly illustrated in FIG. 2 of the Kleven Declaration, however, the level of side effects observed for the three sets of experiments was *not* what was expected. As shown in FIG. 2 of the Kleven Declaration, (S)-norketamine provided 5-fold less ataxia, and (R)-norketamine provided 7-fold less ataxia, compared with racemic ketamine. The two enantiomers also produced significantly less stereotypic behavior compared with racemic ketamine. And as described at paragraph 11 of the Kleven Declaration, "(±)-ketamine was observed to evoke an early (within 5 min) PCP-like behavior (e.g., head weaving, turning) [which] was not observed with S(+)- and R(-)-norketamine at any dose tested."

Therefore, Applicants respectfully contend that the evidence presented in the Kleven Declaration constitute a showing of unexpected results sufficient to overcome any allegation of obviousness. Reconsideration by the Examiner of the evidence presented in the Kleven Declaration is respectfully requested.

III. The Examiner's Proposed Combination Does Not Meet All of the Elements of the Claimed Invention Because the Upper Range of the Claimed Dosage Level Falls Well Below What Can Reasonably be Attributed to the Teachings of Harbut *et al.*

In rejecting Applicants' previous argument that not all of the claimed elements are taught or suggested by the prior art, specifically the dose limitation of 0.01 to about 20 mg/kg of body weight of the patient, the Examiner contends that the Harbut *et al.* reference "clearly

teaches the typical dosage for ketamine is 10 mg/hour (paragraph 0100) or 240 mg per day, which meet the limitation between 0.05 to 8 mg/kg body weight or 3.5 to 1400 mg for an average adult of 70 kg." (Office Action, at the bottom of page 7.) Applicants' respectfully traverse the Examiner's position for the reasons that follow.

First, Applicants, in an effort to advance prosecution of the present application, have amended the upper limit of their claimed dosage range to 8 mg/kg of body weight of the patient, which corresponds to 480 mg for a 60 kg patient (560 mg for a 70 kg patient) of *(S)-norketamine*. Second, while Applicants agree with the Examiner that Harbut *et al.* teach intravenous infusion of 10 mg/hour to a patient, Applicants respectfully point out that such teaching is specifically related to *racemic ketamine*. As discussed in detail above, Applicants point out further that Harbut *et al.* also teach that racemic ketamine is approximately four times as effective as racemic norketamine in reducing pain signals. Accordingly, one of ordinary skill in the art seeking to evoke a similar pharmacologic effect from intravenous infusion of racemic norketamine would have multiplied Harbut *et al.*'s 10 mg/hour intravenous infusion by a factor of four, arriving at an intravenous infusion of 40 mg/hour. Over a twenty-four hour period, that dosage level equates to 960 mg, which is well above Applicants' claimed upper limit.

Moreover, how one of ordinary skill in the art would properly account for the greater *in vitro* binding activity of (S)-norketamine versus (R)-norketamine as described in Ebert *et al.* is a matter of speculation. Because (R)-norketamine retains *some* binding activity (and, presumably, *some* pharmacologic activity) one cannot discount completely its contribution to the reduction of pain signals. Accordingly, even if one were to *guess* at the relative effectiveness of (S)-norketamine compared with that of racemic ketamine, one might arrive at a figure that lies somewhere above 25% *but less than* 50%. Any way one looks at it, Harbut *et al.* teach a dosage level above Applicants' claimed upper limit.

Lastly, because Harbut *et al.* teach a dosage level *via* intravenous infusion, one of ordinary skill in the art seeking to reduce pain signals *via* oral administration of norketamine, would have to further multiply 960 mg by a factor of three or four to account for the decrease in bioavailability of drugs when administered orally. Applicants newly presented claim 84 is limited to an oral mode of administration.

In summary, when properly considered Harbut *et al.* teach a dosage level that falls well above the Applicants' claimed upper limit. Put another way, the upper range of the claimed dosage level falls well below what can reasonably be attributed to the teachings of Harbut *et al.* Having overcome the Examiner's rejection, Applicants respectfully request that the rejection be withdrawn.

Conclusion

Applicants respectfully request reconsideration of the pending claims, which Applicants submit are in condition for allowance. A Notice to that effect is cordially solicited.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,
FOLEY & LARDNER LLP

Date:: 16 Dec 2008
FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5300
Facsimile: (202) 672-5399

By: _____
Gilberto M. Villacorta, PH.D.
Registration No. 34,038